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GOON, SCARLETT Y	
ART UNIT	PAPER NUMBER
1623	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,743	TSUJI ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *2,9,11 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,10,12,13 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *14 March 2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on 20 March 2009 in which claims 1-3 and 5-7 were amended, and claim 15 is newly added, is acknowledged.

Claims 1-14 are pending in the instant application.

Priority

This application is a National Stage entry of PCT/JP2005/005695 filed on 28 March 2005 and claims priority to Japan foreign application 2004-107760 filed on 31 March 2004. Applicants are requested to note that the Office Action dated 23 February 2009 incorrectly indicated that the National Stage entry of PCT/JP2005/005695 was filed on 28 March 2008. A certified copy of the foreign priority document in Japanese has been received. No English translation has been received.

Information Disclosure Statement

The information disclosure statement (IDS) dated 14 March 2008 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Election/Restrictions

Applicant's election with traverse for the compound of formula (1) as the elected species of flavone C-glycosides, in the reply filed on 20 March 2009, is acknowledged. The traversal is on the ground(s) that the Office has not sufficiently showed that it is a burden to search all the species of the claims. This is not found persuasive because

undue search burden is not a criteria for election/restriction purposes under 35 USC §121 and 35 USC § 372. As indicated in the Election/Restriction requirement dated 23 February 2009, the species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1. The compounds of formula (1) and formula (4) are both publicly known, for example, in JP 2004-035474. Therefore, the claims are not considered as being so linked as to form a single general inventive concept and a requirement for an election of species is proper.

The requirement is still deemed proper and is therefore made FINAL.

Claims 2, 9, 11 and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 20 March 2009.

Claims 1, 3-8, 10, 12, 13 and 15 will be examined on its merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "THF" in claim 4 renders the claim herein indefinite. Acronyms or abbreviations can be interpreted differently depending on the context and the art. For example, "EPA" can stand for "eicosapentaenoic acid" or it can be an abbreviation for the "Environmental Protection Agency". Thus, it is unclear whether "THF" refers to tetrahydrofuran, or whether it is an acronym or abbreviation for something else. To render the claim definite, it is respectfully suggested that Applicants spell out what they intend to claim, rather than use acronyms or abbreviations. If Applicants intend to use acronyms or abbreviations in the claims, it is respectfully suggested that the acronym or abbreviation first be spelled out along with the acronym where it is first used in a claim before use of the acronym or abbreviation in subsequent claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Section [0001]

Claims 1, 3, 5-7, 10, 13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2004/005296 to Ishikura *et al.* (PTO-892, Ref. N; PG Pub No. US 2005/0288237 A1 (PTO-892, Ref. A) used as English equivalent for translation), in view of journal publication by Nakatsuka *et al.* (PTO-892, Ref. U), in view of journal publication by Mahling *et al.* (IDS dated 14 March 2008).

Ishikura *et al.* teach a flavone C-glycoside of formula (1) found in oolong tea having anti-allergic effects, and compositions containing the isolated flavone. The flavone C-glycoside of formula (1) is the same compound as formula (1) of the instant claims. Figure 3 also teaches structures of other flavonoids, including isovitexin, which is the starting material used in the method of the instant claims.

Although Ishikura *et al.* teach a flavone C-glycoside of formula (1) and isovitexin, which is structurally similar to the flavone C-glycoside of formula (1) except for

cyclization of the glucoside with the benzopyrone backbone of the flavonoid, Ishikura *et al.* do not disclose any method for the synthesis of the compound of formula (1).

Nakatsuka *et al.* teach a method for the total synthesis of the unique flavonoids denoted as compounds (1a) and (1b). Compound (1a) is the same compound as formula (1) of the instant claims. Cyclization of compound (9) with inversion of the C-2 stereocenter on glucose is accomplished using Mitsunobu conditions to give compound (10) (p. 3202, Scheme 2). The reaction conditions include treatment of compound (9) with 1,1'azobis(*N*,*N*-dimethylformamide) and tributylphosphine in benzene at room temperature. Compound (10) was obtained in a 73% yield.

Mahling *et al.* teach that aryl C-glycosides, and especially flavone C-glycosides, are widespread in nature (p. 461, column 1, paragraph 1). Examples of flavone C-glycosides found in nature include vitexin, isovitexin and isoembigenin.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Ishikura *et al.*, concerning a flavone C-glycoside of formula (1) and its anti-allergic effects, with the teachings of Nakatsuka *et al.*, regarding the cyclization of compound (9) with inversion of the C-2 stereocenter on glucose via Mitsunobu conditions, with the teachings of Mahling *et al.*, regarding the widespread occurrence of flavone C-glycosides such as isovitexin in nature. Since Ishikura *et al.* teach that the compound of formula (1) has anti-allergic effects, one of ordinary skill in the art would have been motivated to synthesize the compound for use in a composition for treating patients with allergies. With regards to using isovitexin as the starting material, one of ordinary skill in the art would have chosen isovitexin since it

is structurally similar to the desired product and, as disclosed by Mahling *et al.*, is widespread in nature, thereby requiring minimal manipulative organic synthetic steps, which would also generate less chemical waste. Since Nakatsuka *et al.* teach the synthesis of the same compound of formula (1), albeit using different steps, starting materials, and intermediates, the resulting product is the same as the compound taught by Ishikura *et al.* Thus, as the key step for cyclization of glucoside with the benzopyrone backbone requires similar structures, one of ordinary skill in the art would reasonably expect that the Mitsunobu method taught by Nakatsuka *et al.* can be applied to isovitexin for the synthesis the compound of formula (1) taught by Ishikura *et al.*

With regards to the limitations of instant claim 10 wherein the product is obtained in over a 40% yield, one of ordinary skill in the art would reasonably expect that since a similar reaction disclosed by Nakatsuka *et al.* was obtained in a 73% yield, the resultant yield for conversion of isovitexin to the compound of formula (1) would also be within a similar range.

With regards to the limitations of claim 13 wherein unreacted isovitexin is recycled, it is considered within the capabilities of one of ordinary skill in the art to determine whether the unreacted isovitexin is of sufficient purity to be recycled in another reaction. It is *prima facie* obvious that using unreacted starting material in another reaction would save on costs.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0002]

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2004/005296 to Ishikura *et al.* (PTO-892, Ref. N; PG Pub No. US 2005/0288237 A1 (PTO-892, Ref. A) used as English equivalent for translation), in view of journal publication by Nakatsuka *et al.* (PTO-892, Ref. U), in view of journal publication by Mahling *et al.* (IDS dated 14 March 2008) as applied to claims 1, 3, 5-7, 10, 13 and 15 above, further in view of journal publication by Mitsunobu (IDS dated 14 March 2008).

The teachings of Ishikura *et al.*, Nakatsuka *et al.*, and Mahling *et al.*, were as disclosed in section [0001] above in the claim rejections under 35 USC § 103.

The combined teachings of Ishikura *et al.*, Nakatsuka *et al.*, and Mahling *et al.* do not explicitly indicate that the organic solvent used in the reaction is THF.

Mitsunobu teach the use of diethyl azodicarboxylate and triphenylphosphine in the synthesis and transformation of natural products. The reaction is carried out in an anhydrous aprotic solvent such as ether or tetrahydrofuran at room temperature or below (p. 2, column 1, first full paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Ishikura *et al.*, concerning a flavone C-glycoside of formula (1) and its anti-allergic effects, with the teachings of Nakatsuka *et al.*, regarding the cyclization of compound (9) with inversion of the C-2 stereocenter on glucose via Mitsunobu conditions, with the teachings of Mahling *et al.*, regarding the widespread occurrence of flavone C-glycosides such as isovitexin in nature, with the

teachings of Mitsunobu, regarding the use of anhydrous aprotic solvents such as ether or tetrahydrofuran in the synthesis and transformation of natural products using diethyl azodicarboxylate and triphenylphosphine. Since the reaction taught by Mitsunobu is the same as that disclosed by Nakatsuka *et al.*, one of ordinary skill in the art would reasonably expect that the substitution of tetrahydrofuran in place of the benzene solvent taught by Nakatsuka *et al.* would still yield the expected product.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0003]

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2004/005296 to Ishikura *et al.* (PTO-892, Ref. N; PG Pub No. US 2005/0288237 A1 (PTO-892, Ref. A) used as English equivalent for translation), in view of journal publication by Nakatsuka *et al.* (PTO-892, Ref. U), in view of journal publication by Mahling *et al.* (IDS dated 14 March 2008) as applied to claims 1, 3, 5-7, 10, 13 and 15 above, further in view of Greene *et al.* (PTO-892, Ref. V).

The teachings of Ishikura *et al.*, Nakatsuka *et al.*, and Mahling *et al.*, were as disclosed in section [0001] above in the claim rejections under 35 USC § 103.

The combined teachings of Ishikura *et al.*, Nakatsuka *et al.*, and Mahling *et al.* do not explicitly indicate that isovitexin is protected by a protecting group.

Greene *et al.* teach that when a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be

temporarily blocked (p. 1). This is accomplished by the use of protecting groups, thereby blocking reactivity at these other reactive sites.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Ishikura *et al.*, concerning a flavone C-glycoside of formula (1) and its anti-allergic effects, with the teachings of Nakatsuka *et al.*, regarding the cyclization of compound (9) with inversion of the C-2 stereocenter on glucose via Mitsunobu conditions, with the teachings of Mahling *et al.*, regarding the widespread occurrence of flavone C-glycosides such as isovitexin in nature, with the teachings of Greene *et al.*, regarding the use of protecting groups to block other functional reactive sites on the same molecule. One would have been motivated to combine the teachings and include a protecting group on isovitexin in order to receive the expected benefit, as taught by Greene *et al.*, that the use of a protecting group would result in a reaction selectively occurring only on one reactive site of a multifunctional compound, thereby minimize unwanted side products that can occur from existing multi-reactive functional groups.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0004]

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2004/005296 to Ishikura *et al.* (PTO-892, Ref. N; PG Pub No. US 2005/0288237 A1 (PTO-892, Ref. A) used as English equivalent for translation), in view

of journal publication by Nakatsuka *et al.* (PTO-892, Ref. U), in view of journal publication by Mahling *et al.* (IDS dated 14 March 2008) as applied to claims 1, 3, 5-7, 10, 13 and 15 above, further in view of journal publication by Amos *et al.* (PTO-892, Ref. W).

The teachings of Ishikura *et al.*, Nakatsuka *et al.*, and Mahling *et al.*, were as disclosed in section [0001] above in the claim rejections under 35 USC § 103.

The combined teachings of Ishikura *et al.*, Nakatsuka *et al.*, and Mahling *et al.* do not explicitly teach that the trialkylphosphine used in the reaction is supported on a styrene resin.

Amos *et al.* teach a method of esterification using a polymer-supported phosphine reagent. The use of triphenylphosphine and diethyl azodicarboxylate, commonly known as the Mitsunobu conditions, is a well established means of forming esters from alcohols and acid and macrolides from precursor ω-hydroxy acids (p. 3598, column 1, first paragraph). The use of polystyryldiphenylphosphine as a reagent in this reaction, in place of triphenylphosphine, affords a convenience in terms of preparation and purification of the product (p. 3598, column 1, first paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Ishikura *et al.*, concerning a flavone C-glycoside of formula (1) and its anti-allergic effects, with the teachings of Nakatsuka *et al.*, regarding the cyclization of compound (9) with inversion of the C-2 stereocenter on glucose via Mitsunobu conditions, with the teachings of Mahling *et al.*, regarding the widespread occurrence of flavone C-glycosides such as isovitexin in nature, with the

teachings of Amos *et al.*, regarding the use of polystyryldiphenylphosphine in place of triphenylphosphine as a reagent in the Mitsunobu reaction. Since the reaction taught by Amos *et al.* is the same as that disclosed by Nakatsuka *et al.*, one of ordinary skill in the art would reasonably expect that the substitution of polystyryldiphenylphosphine in place of the triphenylphosphine reagent taught by Nakatsuka *et al.* would still yield the expected product. Furthermore, one of ordinary skill in the art would be motivated to make the substitution as Amos *et al.* teach that the use of polystyryldiphenylphosphine affords a convenience in terms of preparation and purification of the product.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0005]

Claims 1, 3-7, 10, 13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2004/005296 to Ishikura *et al.* (PTO-892, Ref. N; PG Pub No. US 2005/0288237 A1 (PTO-892, Ref. A) used as English equivalent for translation), in view of WIPO publication WO 2004/092180 to Nakatsuka (IDS dated 14 March 2008; machine translation of JP 2006-176407 (PTO-892, Ref. O) used as English equivalent for translation), in view of journal publication by Mahling *et al.* (IDS dated 14 March 2008).

The teachings of Ishikura *et al.* were as disclosed in section [0001] above in the claim rejections under 35 USC § 103.

Although Ishikura *et al.* teach a flavone C-glycoside of formula (1) and isovitexin, which is structurally similar to the flavone C-glycoside of formula (1) except for cyclization of the glucoside with the benzopyrone backbone of the flavonoid, Ishikura *et al.* do not disclose any method for the synthesis of the compound of formula (1).

Nakatsuka teach a method for the manufacture of a flavone derivative of formula (Ia) which has anti-inflammatory activity (p. 16, paragraph 0002 and 0003). A key step in the synthesis of the compound of formula (Ia) is the dehydrating condensation reaction process accompanied by solid inversion for the conversion of compound (XV) to compound (VI) (p. 26, paragraph 0037). The reaction can be performed by using the Mitsunobu reaction in the presence of trialkylphosphine, such as tributylphosphine, and an azo compound, such as tetramethyl azodicarboxamide (same as instantly claimed 1,1'azobis(*N*,*N*-dimethylformamide)), in benzene (p. 26, paragraph 0038). Other aromatic hydrocarbon solvents, such as toluene, diethylether, chloroform, and tetrahydrofuran, can also be used (p. 26, paragraph 0038).

The teachings of Mahling *et al.* were as disclosed in section [0001] above in the claim rejections under 35 USC § 103.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Ishikura *et al.*, concerning a flavone C-glycoside of formula (1) and its anti-allergic effects, with the teachings of Nakatsuka, regarding the dehydrating condensation reaction of compound (XV) using Mitsunobu conditions, with the teachings of Mahling *et al.*, regarding the widespread occurrence of flavone C-glycosides such as isovitexin in nature. Since Ishikura *et al.* teach that the compound of

formula (1) has anti-allergic effects, one of ordinary skill in the art would have been motivated to synthesize the compound for use in a composition for treating patients with allergies. With regards to using isovitexin as the starting material, one of ordinary skill in the art would have chosen isovitexin since it is structurally similar to the desired product and, as disclosed by Mahling *et al.*, is widespread in nature, thereby requiring minimal organic synthetic steps, which would require less chemical waste. Since Nakatsuka teach the synthesis of the same compound of formula (1), albeit using different steps, starting materials, and intermediates, the resulting product is the same as the compound taught by Ishikura *et al.* Thus, as the key step for the dehydration condensation of glucoside with the benzopyrone backbone requires similar structures, one of ordinary skill in the art would reasonably expect that the dehydration condensation method taught by Nakatsuka can be applied to isovitexin for the synthesis the compound of formula (1) taught by Ishikura *et al.*

With regards to the limitations of instant claim 10 wherein the product is obtained in over a 40% yield, it is noted that Nakatsuka do not disclose the yield obtained from their dehydrating condensation reaction. However, it is considered within the capabilities of one of ordinary skill in the art to optimize the reaction conditions in order to obtain optimal reaction yields. Furthermore, as similar reaction conditions are performed, it is reasonable to expect that a similar yield would result.

With regards to the limitations of claim 13 wherein unreacted isovitexin is recycled, it is considered within the capabilities of one of ordinary skill in the art to determine whether the unreacted isovitexin is of sufficient purity to be recycled in

another reaction. It is *prima facie* obvious that using unreacted starting material in another reaction would save on costs.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0006]

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2004/005296 to Ishikura *et al.* (PTO-892, Ref. N; PG Pub No. US 2005/0288237 A1 (PTO-892, Ref. A) used as English equivalent for translation), in view of WIPO publication WO 2004/092180 to Nakatsuka (IDS dated 14 March 2008; machine translation of JP 2006-176407 (PTO-892, Ref. O) used as English equivalent for translation), in view of journal publication by Mahling *et al.* (IDS dated 14 March 2008) as applied to claims 1, 3-7, 10, 13 and 15, further in view of Greene *et al.* (PTO-892, Ref. V).

The teachings of Ishikura *et al.* and Mahling *et al.* were as disclosed in section [0001] above in the claim rejections under 35 USC § 103 and the teachings of Nakatsuka were as disclosed in section [0005] above in the claim rejections under 35 USC § 103.

The combined teachings of Ishikura *et al.*, Nakatsuka, and Mahling *et al.* do not explicitly indicate that isovitexin is protected by a protecting group.

The teachings of Greene *et al.* were as disclosed in section [0003] above in the claim rejections under 35 USC § 103.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Ishikura *et al.*, concerning a flavone C-glycoside of formula (1) and its anti-allergic effects, with the teachings of Nakatsuka, regarding the dehydrating condensation reaction of compound (XV) using Mitsunobu conditions, with the teachings of Mahling *et al.*, regarding the widespread occurrence of flavone C-glycosides such as isovitexin in nature, with the teachings of Greene *et al.*, regarding the use of protecting groups to block other functional reactive sites on the same molecule. One would have been motivated to combine the teachings and include a protecting group on isovitexin in order to receive the expected benefit, as taught by Greene *et al.*, that the use of a protecting group would result in a reaction selectively occurring only on one reactive site of a multifunctional compound, thereby minimize unwanted side products that can occur from existing multi-reactive functional groups.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0007]

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2004/005296 to Ishikura *et al.* (PTO-892, Ref. N; PG Pub No. US 2005/0288237 A1 (PTO-892, Ref. A) used as English equivalent for translation), in view of WIPO publication WO 2004/092180 to Nakatsuka (IDS dated 14 March 2008; machine translation of JP 2006-176407 (PTO-892, Ref. O) used as English equivalent for translation), in view of journal publication by Mahling *et al.* (IDS dated 14 March

2008) as applied to claims 1, 3-7, 10, 13 and 15, further in view of journal publication by Amos *et al.* (PTO-892, Ref. W).

The teachings of Ishikura *et al.* and Mahling *et al.* were as disclosed in section [0001] above in the claim rejections under 35 USC § 103 and the teachings of Nakatsuka were as disclosed in section [0005] above in the claim rejections under 35 USC § 103.

The combined teachings of Ishikura *et al.*, Nakatsuka, and Mahling *et al.* do not explicitly teach that the trialkylphosphine used in the reaction is supported on a styrene resin.

The teachings of Amos *et al.* were as disclosed in section [0004] above in the claim rejections under 35 USC § 103.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Ishikura *et al.*, concerning a flavone C-glycoside of formula (1) and its anti-allergic effects, with the teachings of Nakatsuka, regarding the dehydrating condensation reaction of compound (XV) using Mitsunobu conditions, with the teachings of Mahling *et al.*, regarding the widespread occurrence of flavone C-glycosides such as isovitexin in nature, with the teachings of Amos *et al.*, regarding the use of polystyryldiphenylphosphine in place of triphenylphosphine as a reagent in the Mitsunobu reaction. Since the reaction taught by Amos *et al.* is the same as that disclosed by Nakatsuka, one of ordinary skill in the art would reasonably expect that the substitution of polystyryldiphenylphosphine in place of the triphenylphosphine reagent taught by Nakatsuka *et al.* would still yield the expected product. Furthermore, one of

ordinary skill in the art would be motivated to make the substitution as Amos *et al.* teach that the use of polystyryldiphenylphosphine affords a convenience in terms of preparation and purification of the product.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0008]

Claims 1, 3-7, 10, 13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2004/005296 to Ishikura *et al.* (PTO-892, Ref. N; PG Pub No. US 2005/0288237 A1 (PTO-892, Ref. A) used as English equivalent for translation), in view of journal publication by Mahling *et al.* (IDS dated 14 March 2008), in view of journal publication by Mitsunobu *et al.* (IDS dated 14 March 2008), in view of journal publication by Dallinger *et al.* (PTO-892, Ref. X).

The teachings of Ishikura *et al.* were as disclosed in section [0001] above in the claim rejections under 35 USC § 103.

Although Ishikura *et al.* teach a flavone C-glycoside of formula (1) and isovitexin, which is structurally similar to the flavone C-glycoside of formula (1) except for cyclization of the glucoside with the benzopyrone backbone of the flavonoid, Ishikura *et al.* do not disclose any method for the synthesis of the compound of formula (1).

Mahling *et al.* teach that aryl C-glycosides, and especially flavone C-glycosides are widespread in nature (p. 461, column 1, paragraph 1). Examples of flavone C-

glycosides found in nature include vitexin, isovitexin and isoembigenin. The chemical synthesis of isovitexin (1b) is further disclosed (p. 463, column 1).

Mitsunobu teach the use of diethyl azodicarboxylate and triphenylphosphine in the synthesis and transformation of natural products. The reaction is carried out in an anhydrous aprotic solvent such as ether or tetrahydrofuran at room temperature or below (p. 2, column 1, first full paragraph) and is useful for esterification and alkylation reactions (see entire reference). The Mitsunobu reaction can be used in the preparation of carbonates (p. 19, section 6.2.5), which are then useful as an alkylating agent. Furthermore, it can be used in self-condensation reactions, such as with macrolides (p. 23).

Dallinger *et al.* teach selective alkylation using Mitsunobu-type conditions. The Mitsunobu reaction is a versatile method for the conversion of aliphatic alcohols into alkylating agents in situ under mild conditions (p. 1901, column 1, last paragraph). The use of classical Mitsunobu reagents which include diethyl azodicarboxylate-triphenylphosphine, are limited to rather acidic nucleophiles. More active Mitsunobu coupling reagents include 1,1'-(azodicarbonyl)dipiperidine and *N,N,N',N'*-tetramethylazodicarboxamide (same as 1,1'azobis(*N,N*-dimethylformamide) of instant claims) in combination with tributylphosphine (p. 1901, column 2, bridging paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Ishikura *et al.*, concerning a flavone C-glycoside of formula (1) and its anti-allergic effects, with the teachings of Mahling *et al.*, regarding the widespread occurrence of flavone C-glycosides such as isovitexin in nature, with the

teachings of Mitsunobu, regarding the use of diethyl azodicarboxylate and triphenylphosphine in the synthesis and transformation of natural products, with the teachings of Dallinger *et al.*, regarding the use of Mitsunobu-type conditions for the conversion of aliphatic alcohols into alkylating agents *in situ*. Since Ishikura *et al.* teach that the compound of formula (1) has anti-allergic effects, one of ordinary skill in the art would have been motivated to synthesize the compound for use in a composition for treating patients with allergies. With regards to using isovitexin as the starting material, one of ordinary skill in the art would have chosen isovitexin since it is structurally similar to the desired product and its method of synthesis has already been disclosed by Mahling *et al.*, thereby requiring minimal additional manipulative organic synthetic steps to generate the desired product. Having possession of isovitexin and desiring to synthesize the flavone C-glycoside of formula (1) disclosed by Ishikura *et al.*, an ordinarily skilled organic chemist would be able to determine that the conversion can be achieved by a Mitsunobu reaction, which Mitsunobu and Dallinger *et al.* teach is used for conversion of alcohols into alkylating agents *in situ*. With regards to the use of *N,N,N',N'*-tetramethylazodicarboxamide in combination with tributylphosphine, one of ordinary skill in the art would have been motivated to choose these reagents since Dallinger *et al.* teach that these reagents are more reactive than the classical Mitsunobu set of reagents.

It is noted that the combined teachings of the prior art do not explicitly disclose the limitations of instant claim 10 wherein the product is obtained in over a 40% yield.

However, as the same reaction is performed under similar conditions, it is reasonable to expect that one of ordinary skill in the art would arrive at a similar reaction yield.

With regards to the limitations of claim 13 wherein unreacted isovitexin is recycled, it is considered within the capabilities of one of ordinary skill in the art to determine whether the unreacted isovitexin is of sufficient purity to be recycled in another reaction. It is *prima facie* obvious that using unreacted starting material in another reaction would save on costs.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0009]

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2004/005296 to Ishikura *et al.* (PTO-892, Ref. N; PG Pub No. US 2005/0288237 A1 (PTO-892, Ref. A) used as English equivalent for translation), in view of journal publication by Mahling *et al.* (IDS dated 14 March 2008), in view of journal publication by Mitsunobu (IDS dated 14 March 2008), in view of journal publication by Dallinger *et al.* (PTO-892, Ref. X) as applied to claims 1, 3-7, 10, 13 and 15 above, further in view of Greene *et al.* (PTO-892, Ref. V).

The teachings of Ishikura *et al.* were as disclosed in section [0001] above, and the teachings of Mahling *et al.*, Mitsunobu, and Dallinger *et al.* were as disclosed in section [0008] above, in the claim rejections under 35 USC § 103.

The combined teachings of Ishikura *et al.*, Mahling *et al.*, Mitsunobu, and Dallinger *et al.* do not explicitly indicate that isovitexin is protected by a protecting group.

The teachings of Greene *et al.* were as disclosed in section [0003] above in the claim rejections under 35 USC § 103.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Ishikura *et al.*, concerning a flavone C-glycoside of formula (1) and its anti-allergic effects, with the teachings of Mahling *et al.*, regarding the widespread occurrence of flavone C-glycosides such as isovitexin in nature, with the teachings of Mitsunobu, regarding the use of diethyl azodicarboxylate and triphenylphosphine in the synthesis and transformation of natural products, with the teachings of Dallinger *et al.*, regarding the use of Mitsunobu-type conditions for the conversion of aliphatic alcohols into alkylating agents *in situ*, with the teachings of Greene *et al.*, regarding the use of protecting groups to block other functional reactive sites on the same molecule. One would have been motivated to combine the teachings and include a protecting group on isovitexin in order to receive the expected benefit, as taught by Greene *et al.*, that the use of a protecting group would result in a reaction selectively occurring only on one reactive site of a multifunctional compound, thereby minimize unwanted side products that can occur from existing multi-reactive functional groups.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0010]

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2004/005296 to Ishikura *et al.* (PTO-892, Ref. N; PG Pub No. US 2005/0288237 A1 (PTO-892, Ref. A) used as English equivalent for translation), in view of journal publication by Mahling *et al.* (IDS dated 14 March 2008), in view of journal publication by Mitsunobu (IDS dated 14 March 2008), in view of journal publication by Dallinger *et al.* (PTO-892, Ref. X) as applied to claims 1, 3-7, 10, 13 and 15 above, further in view of journal publication by Amos *et al.* (PTO-892, Ref. W).

The teachings of Ishikura *et al.* were as disclosed in section [0001] above, and the teachings of Mahling *et al.*, Mitsunobu, and Dallinger *et al.* were as disclosed in section [0008] above, in the claim rejections under 35 USC § 103.

The combined teachings of Ishikura *et al.*, Mahling *et al.*, Mitsunobu, and Dallinger *et al.* do not explicitly indicate that the trialkylphosphine used in the reaction is supported on a styrene resin.

The teachings of Amos *et al.* were as disclosed in section [0004] above in the claim rejections under 35 USC § 103.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Ishikura *et al.*, concerning a flavone C-glycoside of formula (1) and its anti-allergic effects, with the teachings of Mahling *et al.*, regarding the widespread occurrence of flavone C-glycosides such as isovitexin in nature, with the teachings of Mitsunobu, regarding the use of diethyl azodicarboxylate and triphenylphosphine in the synthesis and transformation of natural products, with the

teachings of Dallinger *et al.*, regarding the use of Mitsunobu-type conditions for the conversion of aliphatic alcohols into alkylating agents *in situ*, with the teachings of Amos *et al.*, regarding the use of polystyryldiphenylphosphine in place of triphenylphosphine as a reagent in the Mitsunobu reaction. Since the reaction taught by Amos *et al.* is the same as that disclosed by Mitsunobu and Dallinger *et al.*, one of ordinary skill in the art would reasonably expect that the substitution of polystyryldiphenylphosphine in place of the triphenylphosphine or tributylphosphine reagent taught by Mitsunobu and Dallinger *et al.* would still yield the expected product. Furthermore, one of ordinary skill in the art would be motivated to make the substitution as Amos *et al.* teach that the use of polystyryldiphenylphosphine affords a convenience in terms of preparation and purification of the product.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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